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Stereodefined *N,O*-Acetals: Pd-Catalyzed Synthesis from Homopropargylic Amines and Utility in the Flexible Synthesis of 2,6-Substituted Piperidines

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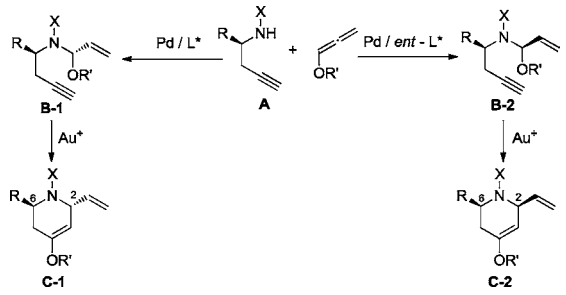
Supporting Information

ABSTRACT: We developed a conceptually new synthetic strategy which exploits the stereochemical information of labile acyclic *N,O*-acetals. The key to this strategy, chemo- and stereoselective synthesis of *N,O*-acetals, was achieved by the Pd-catalyzed addition of sulfonyl-protected homopropargylic amines to alkoxyallene. The *N,O*-acetals generated in this way were combined with Au-catalyzed cycloisomerization to give an access to 2,6-disubstituted piperidines with stereochemical flexibility.

Mixed acetals are recognized as key intermediates for many synthetically useful organic transformations. In particular, acyclic *N,O*-acetals have been conceived as a precursor for the iminium ion mediated C−C bond formation.[1] In most studies reported in this area, the stereochemical information of the *N,O*-acetal has attracted little attention from the synthetic chemists,[2] presumably due to the instability of the *N,O*-acetals.[3] Because of this inherent problems, the reactions that directly utilize the stereochemistry of *N,O*-acetals are rare.[4] Unlike the conventional approach described above, we hypothesized that the stereochemically well-defined acyclic *N,O*-acetals could provide unique opportunities in developing new C−C bond formation. This unprecedented strategy requires solutions to two challenging problems. First, the stereocontrolled synthesis of acyclic *N,O*-acetals is very limited.[5] Moreover, the utility of the stereodefined *N,O*-acetals needs to be verified. Because the configuration of the *N,O*-acetal carbon must be retained in these transformations, a critical issue in this new approach is the chemoselectivity of the reactions that allows the stereocontrol both in the synthesis and further utilization of the *N,O*-acetals.

Scheme 1 depicts the first example that successfully demonstrates the concept discussed above. We first envisioned the synthesis of stereochemically well-defined *N,O*-acetals **B** via Pd-catalyzed intermolecular addition of chiral homopropargylic amine **A** to alkoxyallene. Numerous examples have been reported for the metal-catalyzed addition of amine nucleophiles to unsaturated C−C bonds.[6,7] However, the proposed reaction is particularly challenging because of the instability of the *N,O*-acetals. We also reasoned that the stereodefined *N,O*-acetals can be combined with the Au-catalyzed racemization-free cycloisomerization[8] to give **C**, where the stereochemical information of *N,O*-acetal is transferred to the iminium ion mediated C−C bond formation.[9,10] From a synthetic viewpoint, this event would introduce the substituents at the 2- and 6-positions of the piperidine framework in a stereochemically flexible manner. Because this structures is easily found in numerous natural products,[11] the proposed strategy should have a unique advantage in the synthesis of bioactive natural products and analogues.

Scheme 1. Synthesis of Stereodefined *N,O*-Acetal and Application



For the synthesis of stereodefined *N,O*-acetals shown in Scheme 1, the ligand-directed selectivity must override the inherent chiral information of the substrate. Thus, various achiral ligands were first explored using tosyl- or nosyl-protected chiral homopropargylic amines (substrates **1** and **2**) and methoxyallene.[12] Indeed, all attempts in varying the reaction conditions gave an ∼1:1 mixture of diastereomeric **4a** and **4b**. Having confirmed that the stereogenic center in the substrate had no effect on the diastereoselectivity, we switched to the chiral ligand-directed approach using the ligand (*R,R*)-**3** as the source of the stereoinduction (Table 1). This is undoubtedly a challenging task, because the intermolecular (ligand-directed) asymmetric hydroamination of allenes still remains unknown, to our best knowledge.[13] Even though Pd-catalyzed asymmetric hydrocarbonation of benzoxyallene has been reported,[14,15] we were concerned that the thermodynamic and kinetic behavior of the hydroamination might be more complicated than the hydrocarbonation. Indeed, our initial efforts were met only with unfruitful results. Reaction of Ns-protected substrate **1** with methoxyallene (3 equiv) in the presence of $Pd(OAc)_2$ (5 mol %), chiral ligand (*R,R*)-**3** (10 mol %), and triethylamine (1.5 equiv) showed poor selectivity, even though the yield was satisfactory (entry 1). The use of additives

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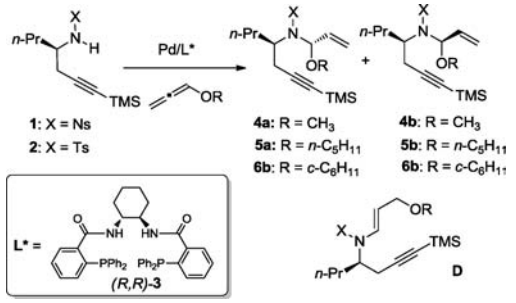
Table 1. Optimization of the Pd(0)-Catalyzed Hydroamination Reaction[a,b]



Entry	X	R	Rxn time (h)	Product	Yield[c] (a:b)[d]
1	Ns	CH_3 (3)	20	**4**	83 (1.3:1)
2[e]	Ns	CH_3 (3)	20	**4**	87 (1.5:1)
3	Ts	CH_3 (3)	20	**4**	12[f] (1.9:1)
4	Ts	CH_3 (30)	40	**4**	95 (6.2:1)
5	Ts	CH_3(70)	20	**4**	92 (10:1)
6	Ts	n-C_5H_{11}(70)	13	**5**	98 (24:1)
7	Ns	n-C_5H_{11}(70)	20	**5**	98 (4:1)
8[g]	Ts	n-C_5H_{11}(70)	13	**5**	99 (1:24)
9	Ts	c-C_6H_{11}(70)	13	**6**	99 (25:1)
10[g]	Ts	c-C_6H_{11}(70)	13	**6**	99 (1:25)

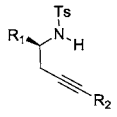
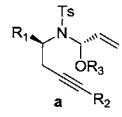
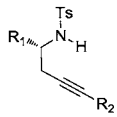
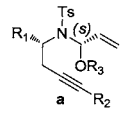
[a]Typical procedure: a mixture of substrate, alkoxyallene, $Pd(OAc)_2$ (5 mol %), (*R,R*)-**3** (10 mol %), and Et_3N (1.5 equiv) was reacted in CH_2Cl_2 at rt. [b]For more detailed information on the optimization, see the Supporting Information. [c]Isolated yield. [d]Determined by the integration of ^1H NMR data. [e]TBAB (4 mol %) was used as an additive. [f]Starting material was recovered in 87% yield. [g]Ligand (*S,S*)-**3** was used.

such as TBAB (tetra-*n*-butylammonium bromide)[16] and trifluoroacetic acid,[14] which are known to facilitate asymmetric allylic substitution, little improved the selectivity (entry 2). In view of this disappointing preliminary result, we surmised that the labile *N,O*-acetal product could be destroyed with concomitant formation of the π-allyl intermediate under the reaction conditions. Apparently, this undesired process that can potentially lower the diastereoselectivity will be facilitated by good leaving groups.

Based upon this analysis, we switched to homopropargylic amine **2** possessing the more basic *p*-toluenesulfonyl (Tosyl) group. In this case, however, the conversion was poor even though the selectivity slightly improved (entry 3). Quite interestingly, a significant increase in both yield and selectivity arose when excess methoxyallene was employed. For example, using 30 equiv of methoxyallene gave the desired *N,O*-acetal **4** in 95% yield with 6.2:1 selectivity (entry 4). Further increasing the amount of methoxyallene to 70 equiv improved the selectivity to ~10:1 with no negative effect on the yield (entry 5). At this point, we reasoned that the nature of the alkoxy group might also be important, because the alkoxy group is in close proximity to the attacking sulfonamide nucleophiles. Indeed, using 70 equiv of *n*-pentoxyallene gave **5a** in near-quantitative 98% yield with ~24:1 selectivity (entry 6). It should be noted that the excess amount of pentoxyallene (>60 equiv) could be easily recovered after the reaction by distillation or column chromatography. Unlike the Ts-protected propargylic amine **2**, Ns-protected amine **1** still showed low selectivity even in the presence of excess alkoxyallene, emphasizing again the significance of the nature of the amine protective group (entry 7). Using the enantiomeric chiral ligand (*S,S*)-**3** gave the diastereomeric *N,O*-acetal **5b** as the exclusive isomer (entry 8) with no decrease in the yield and diastereomeric ratio, supporting our hypothesis that the chiral ligand-derived stereoinduction dominates over the pre-existing stereochemical information of the substrate. Employing bulkier cyclohexyloxyallene still maintained the stereoselectivity to produce **6** (entries 9, 10). Thus, the hydroamination tolerates the steric hindrance of the alkoxyallene. Notably, the linear isomer **D**, which is generated from the attack of the sulfonamide nucleophile to the terminal carbon of the alkoxyallene, could not be detected under the reaction conditions.

Using the optimized conditions in Table 1, an array of tosyl-protected homopropargylic amines were coupled with *n*-pentoxyallene to produce the corresponding *N,O*-acetals (Table 2). Introducing the bulkier isopropyl group at the homopropargylic position maintained high yield and the diastereoselectivity (entry 1), while using the smaller methyl group somewhat decreased the selectivity (entry 2). In addition, diverse functional groups such as phenyl (entry 3),

Table 2. Scope of the Pd(0)-Catalyzed *N,O*-Acetal Formation[a]

Entry	Substrate	Product	Method[b]	Yield(%)[c] (a:b)[d]
				
1	**7** (R_1=*i*-Pr; R_2=TMS)	**12** (R_3=C_5H_{11})	A	99(21:1)
			B	95(>1:25)
2	**8** (R_1=CH_3; R_2= TMS)	**13** (R_3=C_5H_{11})	A	99(19:1)
			B	98(1:16)
3	**9** (R_1= Ph; R_2=H)	**14** (R_3=C_5H_{11})	A	96(25:1)
			B	95(1:21)
4	**10** (R_1= $(CH_2)_6OBn$; R_2= H)	**15** (R_3=C_5H_{11})	A	99(>25:1)
			B	99(>1:25)
5	**11** (R_1=CH_2Ph R_2= TMS)	**16** (R_3=C_5H_{11})	A	96(>25:1)
			B	99(>1:25)
6	**11** (R_1=CH_2Ph R_2= TMS)	**17** (R_3=CH_3)	A	99(14:1)
			B	99(1:13)
				
7	*ent*-**11** (R_1=CH_2Ph R_2= TMS)	**18** (R_3=CH_3)	A	95(13:1)

[a]Typical procedure: a mixture of substrate, alkoxyallene (70 equiv), $Pd(OAc)_2$ (5 mol %), ligand (10 mol %), and Et_3N (1.5 equiv) was reacted in CH_2Cl_2. [b]Method A: Ligand (*R,R*)-**3** was used. Method B: Ligand (*S,S*)-**3** was used. [c]Isolated yield. [d]Determined by the integration of ^1H NMR.

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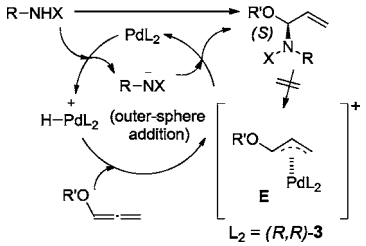
benzylic ether (entry 4), and benzyl group (entries 5, 6) did not interfere with the reaction. Notably, terminal alkynes showed little effect on the rate and selectivity, as illustrated by the reaction of substrates **9** and **10**. To ensure again that the stereoselectivity in the hydroamination is solely determined by the chirality of the ligand, we investigated the substrate *ent*-**11** for the hydroamination reaction. The reaction with methoxyallene under the optimized conditions using the (*R,R*)-**3** ligand gave the *N,O*-acetal **18a** in comparable yield with a somewhat lower 13:1 selectivity (entry 7). Gratifyingly, the absolute structure of **18a** could be unambiguously established by X-ray crystallographic analysis, as depicted in Table 2 (for detailed data, see the Supporting Information (SI)). Moreover, the ^{1}H NMR spectrum of the **18a** was clearly distinguishable from diastereomeric *N,O*-acetal **17a** and identical to the enantiomeric **17b** generated from substrate **11** (entry 6 vs 7). This analysis rigorously confirms the structural assignment of the various *N,O*-acetals generated in Table 1 derived from the chiral ligand-directed hydroamination reaction.

Based upon the above experimental results, a plausible mechanism of the Pd-catalyzed stereoselective hydroamination reaction can be suggested (Scheme 2). As it is consistent with

Scheme 2. Mechanism of the Hydroamination

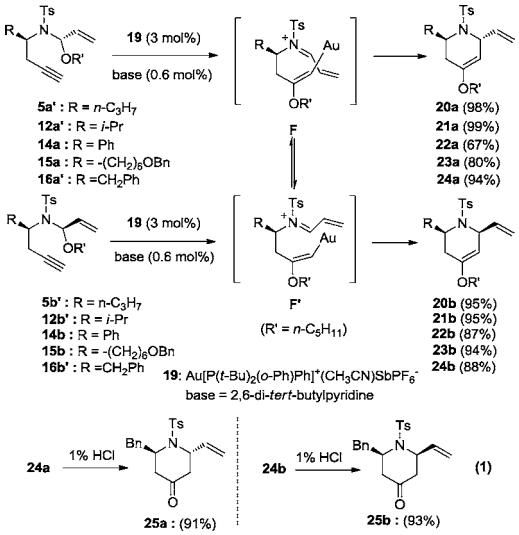


other reports on the Pd-catalyzed hydrocarbonation of allene,[14,15] π-allyl species **E** seems to be involved as the reactive intermediate. Addition of the anion of the sulfonamide to this intermediate then forms the product *N,O*-acetal with regeneration of the Pd catalyst. The π-allyl formation may be promoted by the hydropalladation of the alkoxyallene, as shown in Scheme 2. Alternatively, the oxidative addition of Pd into the N–H bond of sulfonamide could initiate the π-allyl formation. Currently, the exact mechanism for the stereoselectivity is unclear and awaits further studies. Nevertheless, the experimental fact that the (*S*)-configuration arises at the *N,O*-acetal by using ligand (*R,R*)-**3** fits reasonably well into the general model developed for the asymmetric allylic substitution reaction directed by this type of ligand.[16,17] Thus, the formation of stereodefined *N,O*-acetal could be reasonably explained by the outer-sphere addition of the amine nucleophile to the syn isomer of the π-allyl intermediate (**E**).[18]

According to the generally accepted mechanism for the enantioselective intermolecular allylic substitution reaction, slow nucleophilic addition to the π-allyl complex generally increases the enantioselectivity of the reaction. The experimental result in this study that the Ts-protected substrates show higher selectivity than the Ns-protected analogs is apparently inconsistent with this general pattern. This seemingly unusual behavior of the sulfonamide nucleophile **1** vs **2** may address the importance of suppressing the π-allyl formation from the *N,O*-acetal product in achieving high ligand-controlled stereoselectivity. Currently, the origin of the beneficial effect of excess alkoxyallene is unclear. On the basis of the above discussion, it might simply suppress the undesired decomposition of the product *N,O*-acetal shown in Scheme 2.

Having established the access to stereodefined *N,O*-acetals, we then explored the flexible 2,6-disubstituted piperidine formation. As shown in Scheme 3, employing commercially

Scheme 3. Gold-Catalyzed Cycloisomerization



available cationic gold complex **19** (3 mol %) and 2,6-di-*tert*-butylpyridine (0.6 mol %) gave various enol ethers in good to excellent yields. Remarkably, the products were obtained with excellent stereochemical transfer from the corresponding *N,O*-acetals in all cases. For structural analysis, compound **24a** was converted into *cis*-piperidin-4-one **25a** by treatment with catalytic aqueous HCl[19] in 91% yield with no erosion of the stereochemical integrity. Also, diastereomeric *N,O*-acetal **24b** was successfully converted into *trans*-piperidin-4-one **25b** in 93% yield with complete retention of the stereochemistry (eq 1).[20,21]

Based upon our report on the Au-catalyzed formal alkyne aza-Prins reaction,[8] the mechanism of the cycloisomerization seems to involve formation of the iminium ions **F** and **F′** as the reactive intermediate (Scheme 3). The stereochemical transfer in the cycloisomerization strongly suggests the conservation of the iminium ion geometry during the cycloisomerization. This is quite surprising because the (*E*)/(*Z*) isomerization of the iminium ions is known to be a fast process.[2] Thus, this work represents a rare example where the geometry of the iminium ion is successfully controlled. It should be also noted that the cationic Au(I) species were uniquely beneficial for the desired cycloisomerization. Using other (oxophilic) metal catalysts showed epimerization of the *N,O*-acetals and formation of the linear isomer of the *N,O*-acetals (analogous to **D**, Table 1).

In summary, we developed a new Pd-catalyzed synthesis of stereodefined *N,O*-acetals. Moreover, we established the utility of *N,O*-acetals by chemoselective Au-catalyzed cycloisomerization. Mechanistic investigation as well as expansion of the utility of stereodefined *N,O*-acetals in flexible azacycle synthesis is currently in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(21) The terminal alkyne derived from cyclohexyl *N,O*-acetal **6a** and **6b** (Table 1) showed poor conversion in the gold-catalyzed cycloisomerization.